First Total Synthesis of (±)-Ingenol

**Problem:**

1. Propose a mechanism for the transformation from 1 to 2 and explain the high stereoselectivity of the Michael reaction \((\text{R})(\text{S}) = 14:1\).

2. Propose conditions for the formation of 3 starting from the alcohol derived from the ester of 2. (3 steps)

3. Give the structure of cycloheptanes 5 and 7. (What is the role of \(\text{Et}_3\text{N(Bn)Cl}\) in the reaction from 6 to 7?)

4. Propose a mechanism for the transformation of the photoadduct 5 to 6.
Solution:

1. Selectivity of the Michael reaction:
The *cis* configuration of the rings resulted from addition of the crotonate to the sterically less hindered β face of the enolate derived from 1.
The stereochemical outcome can be rationalised by examination of the diastereomeric chelated transition state structures A and B (Heathcock-Seebach model).

While both A and B experience interactions between the crotonate and the enolate, conformer B also suffers from an unfavourable steric interaction between the crotonate α-proton and the C-4 methine of the enolate leading to the preferential formation of 2 from conformer A.

3. Phase Transfer Catalyst
References: